Results of Chemotherapy with BFM-87 Protocol in Children with Acute Myeloid Leukemia at a Referral Center in the Southwest of Iran: Clinical Characteristics and Outcome

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Abstract

Introduction: Leukemia is the most common malignancy in childhood, and acute myeloid leukemia (AML) is the second most common leukemia. AML still accounts for more than 30% of deaths from leukemia. AML is classified into several subgroups from M0 to M7 with different presentations, clinical features, and outcomes.

Material and Methods: Between March 1996 and October 2003, 47 children with acute myeloid leukemia were treated with intensive chemotherapy using BFM-87 protocol after remission at Shafa hospital, Ahwaz, Iran. We compared the presenting features and outcomes of therapy in these children based on age, initial White Blood Cells (WBC) count, Central Nervous System involvement, FAB system types, and response to first induction treatment.

Results: Younger children were more likely to have favourable risks and less likely to have induction deaths (p=0.03) and lower relapse risks (p=0.001). FAB types M2 and M4 showed a better first remission rate (p=0.01, p=0.02, respectively), regardless of age and gender. Two major risk factors for relapse after first remission were initial high WBC counts (p=0.01) and older age at the time of diagnosis (p=0.02). Overall survival (p=0.001), event-free survival (p=0.001), and disease-free survival were better (p<0.001) in younger children due to lower relapse rates (p=0.001).

Discussion: Overall survival was 53% in the children with new AML who were on intensive chemotherapy with a median follow-up time of 5 years in our study. Relapse risk after first remission for the children who were on intensive chemotherapy alone was 34% in our study.

Conclusion: Because of the potential morbidity and mortality usually related to allogeneic HSCT and also problems due to lack of sufficient HSCT possibility for some patients, several cooperative group trials now do not recommend HSCT for good- or standard- risk patients in their first remission. Results of our study were compatible with BFM , AML 10 and AML 12 groups trials in terms of overall survival, or relapse risk, or induction death risk factors.

Keywords: acute myeloid leukemia, survival, chemotherapy

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Introduction

Acute Myeloid Leukemia (AML) is characterized by an increase in the number of myeloid cells in the marrow and an arrest in their maturation, frequently resulting is hematopoietic insufficiency (granulocytopenia, thrombocytopenia, or anemia), with or without leukocytosis[9,17]. Normal hematopoiesis is a complex by which primitive hematopoietic stem cells develop along a multistep pathway into fully differentiated, functionally active circulating blood cells[9,17]. The molecular pathogenesis of AML remains incompletely understood but is clearly linked to the differentiation stage of the transforming events[10,17]. AML is a heterogeneous disease in its clinical manifestations, response to therapy, and molecular genetics, and insight into cell of origin would have important ramifications for diagnosis and treatment [11,17].

The original classification schema required 30% myeloblasts in the bone marrow for the diagnosis of AML but the new World Health Organization (WHO) classification accepts the presence of ≥ 20% bone marrow myeloblasts to be sufficient for diagnosis of AML with some exeptions[2,17]. Although AML comprises only about 15% to 20% of childhood leukemia, it still accounts for more than 30% of deaths from leukemia[3,17]. The comprehensive morphologic classification schema, published in the mid-1970s, was the French-American-British (FAB) system, defining different types of AML as M1 to M7[4]. The role of immunophenotyping study has taken on an increasingly important role in the diagnosis of leukemia and monitoring the response to therapy [5,6,7,8]. AML develops as a result of genetic changes that occur in primitive hematopoietic precursor cells resulting in the expansion of leukemic cells often displaying an incomplete block in normal differentiation [12,13,14]. When Farber et al. used the anti-metabolite aminopterin in 1948 to induce partial remission in children with Acute Lymphocytic Leukemia (ALL), a burst of activity and financial support through government agencies led to introduction of new chemotherapeutic agents for AML, notably cytarabine and anthracyclines [15,3,17]. Nearly all children and adolescents with AML used to die before 1970s [16]. The 1970s saw the introduction of controlled, clinical trials with single and then combination chemotherapeutic agents[16,17]. The results of these approaches from the 1970s and 1980s led to overall cure rates of 25-35% in children and adolescents with AML [16,3].

Based on the partial success of these approaches, clinical trials in the pediatric cooperative groups in 1990s continued to intensify chemotherapy timing or length of exposure as well as utilizing Hematopoietic Stem Cell Transplantation (HSCT) [17]. Given the potential for improved disease control and the potential complications of transplantation, significant questions are when and to which patients should allogeneic HSCT be offered [18,19,20]. Based on most studies, allogeneic hematopoietic stem cell rescue compared to intensive chemotherapy has shown an improved disease-free survival (DFS), overall survival (OS), and decreased relapse risk in children with AML[20,21]. In our study, we evaluated the results of 5 years of intensive chemotherapy alone in children with newly diagnosed AML who did not have HLA-matched donors for HSCT at Shafa hospital, Ahwaz, Iran.

Patients and Methods

Between March 1996 and October 2003, the children (age under 15 years at diagnosis) with AML after the first induction of remission who had no possibility for allogeneic HSCT were eligible for this study. Between March 1996 and October 2003, 55 children were diagnosed with AML at Shafa hospital, a referral pediatric oncology center in the southwest of Iran. A total of 47 eligible patients entered our study. All patients, after documented diagnosis of AML by bone marrow morphology examination and specific staining studies and also immunophenotyping studies or flowcytometry, received intensive chemotherapy for the induction of remission based on BFM-87 protocol. Presence of ≥ 30% myeloblasts in bone marrow was considered sufficient for the diagnosis of AML in our patients. The most commonly employed histochemical stainings along with morphologic classifications were carried out for all patients. We used histochemical staining with peroxidase, Sudan Black B, periodic acid-Schiff, nonspecific esterase, and chloroacetate esterase to distinguish AML and also its subtypes. Immunophenotyping studies to detect specific cell surface expressions through flowcytometry staining were also done for all patients. After documenting the diagnosis of AML and control of bleeding, correction of anemia, reduction of initial high WBC counts and treatment of tumor lysis syndrome in patients if present, intensive chemotherapy started as soon as possible.

All children were scheduled to receive intensive chemotherapy (cytarabine and doxorubicin) in the induction period according to BFM-87 protocol (figure 1).

The children (8 of 55) with an HLA-matched related donor were eligible for allogeneic HSCT after first remission. A total of 47 eligible children who had no possibility for HSCT after their first remission continued intensive chemotherapy with consolidation and also maintenance according to BFM-87 protocol. Central Nervous System (CNS) prophylaxis treatment with intrathecal methotrexate was done for all the patients who underwent chemotherapy in induction and consolidation periods. CNS involvement was defined as the presence of $5x10^6$ blast cells or more per litre of cerebrospinal fluid or isolated cranial nerve palsy. Children with CNS involvement at the time of diagnosis of AML and also the children with CNS relapse received weekly intrathecal chemotherapy with cytarabine and methotrexate and hydrocortisone-based for 6 weeks and then monthly during the maintenance treatment until 6 months. The children older than 3 years with

CNS involvement at the time of diagnosis or CNS relapse who were not scheduled for HSCT also received 24-Gy craniospinal radiation. Bone marrow morphology examination was performed at the end of the first induction chemotherapy course for all patients to insure remission. In children who were scheduled to continue intensive chemotherapy, bone marrow morphology examination was repeated after completing the two consolidation courses. Cytogenetic studies along with clinical presentation, morphology, histochemistry, immunophenotyping are important for identifying the subtypes of AML and also prognosis. Because of lack of cytogenetic studies in our patients, we could not evaluate this factor in our study. In this study, the patients were classified into three groups based on age at the time of diagnosis, initial white blood cells (WBC) counts, CNS involvement at the time of diagnosis, response to first induction chemotherapy, and FAB system types. Good prognostic features include age ≤ 2 years at the time of diagnosis, initial WBC counts less than $100,000x10^9/L$, no CNS involvement at diagnosis, less than 5% bone marrow blasts at the end of the first course of chemotherapy and M3FAB subtype. Poor prognostic features include age older than 2 years at the time of diagnosis, initial WBC count≥$100,000x10^9/L$ (definied as hyperleukocytosis), CNS involvement at the time of diagnosis, no remission or more than 15% blasts at the end of the first course of chemotherapy. All other children are included in the intermediate prognostic group.

Definitions of end points

Complete remission (CR) was defined as a normocellular bone marrow examination containing less than 5% blast cells with normal maturation of other marrow elements and blood count. Remission failure was classified as either induction death, that is, due to treatment or hypoplasia or both, or as resistant disease, that is, failure of therapy to eliminate the disease (including partial remission with 5%-15% blasts). Deaths within 30 days of entry were classified as induction deaths. Overall survival (OS) was defined as the time from diagnosis until death and event-free survival (EFS) as the time from diagnosis until the first event (failure to achieve CR, death in remission or relapse). For patients who achieved remission, disease-free survival (DFS) was the time from CR to death in the first remission or relapse, and risk of relapse was the cumulative risk of relapse from remission, censoring at death in remission.

Statistical methods

To investigate changes in the pattern of the disease and the outcome of treatment, children were subdivided into two age groups: children ≤ 2 years olds and children older than 2 years olds. Clinical features at the time of diagnosis, first remission rate, relapse rate, death in induction, death in relapse, OS, DFS, EFS were compared between the age groups using MINITAB 14 software. Median follow-up was 5 years (range: 3 days to 11 years and 6 months).The exclusion of the child with Down's syndrome and that with secondary AML made no significant difference in the results.

Results

Between March 1996 and October 2003, 55 children were diagnosed with AML. Of them, 47 eligible children were included in this study. Features at presentation are shown in table 1. They were 25 boys and 22 girls, 45 with de novo AML, 1 with secondary AML in a known case of aplastic anemia, 1 with Down's syndrome associated AML. Male to female ratio was 1.1 and mean age at the time of diagnosis was 7.2 years (ranging from 0.5 to 15 years). Comparison between presenting features showed that fever (93%), hepatosplenomegaly (72%), bone pain (59%) and bleeding (53%) were major clinical findings in our patients.

FAB types M2 (32%) and M4 (30%) were more frequent in children. FAB type M2 and M4 showed higher first remission rates (p=0.01, p=0.02, respectively) regardless of age or gender. There was a significant difference in OS (p=0.001), EFS (p=0.001) and DFS (p<0.001) in children ≤ 2 years due to fewer relapses (p=0.001). There was a significant trend in induction deaths with bleeding at presentation (p=0.007), older age (older than 2 years) at the time of diagnosis (p=0.03), and initial hyperleukocytosis (WBC≥$100,000x10^9/L$,(p=0.01). There was a significant trend in deaths after relapse with older age at the time of diagnosis of AML (p=0.002), and with initial hyperleukocytosis (p=0.01). There was no sex-related trend in clinical features (p=0.9), FAB types (p=0.3), initial WBC count (p=0.5), CNS involvement at diagnosis (p=0.1), and first remission rate (p=0.3). There was a trend of relapse with age older than 2 years (p=0.001) and hyperleukocytosis (WBC ≥$100,000x10^9/L$ at the time of the diagnosis of AML (p=0.01), and tumor lysis syndrome during the first course of chemotherapy (p=0.02). There were significant differences in CNS involvement at the time of diagnosis with age (p=0.04), or initial WBCs count (p=0.02). Significant adverse risk factors for relapse

were age older than 2 years (p=0.001), and initial hyperleukocytosis (p=0.01) at the time of the diagnosis of AML. Significant risk factors for deaths in induction were age older than 2 years (p=0.03), and presence of bleeding (p=0.007) at the time of the diagnosis of AML. There were 13 deaths in the induction period and 9 deaths after relapse in our study. Overall Sepsis (82%) and disseminated intravascular coagulation (65%) were major causes of deaths during induction in our study. Major risk factors for bone marrow relapse were age older than 2 years (p=0.001), and hyperleukocytosis(p=0.01) at the time of the diagnosis of AML. DFS, and EFS were better in the good prognostic group (p<0.001, p=0.001, respectively). In multivariate analysis, age was a major factor for bone marrow relapse (higher in those older than 2 years, p=0.001), induction deaths (better prognosis in those aged ≤ 2 years, p=0.03), CR rate (worse prognosis in those aged older than 2 years, p=0.001), and also DFS (worse prognosis in those aged older than 2 years, p=0.001). There was no significant difference in time to relapse or site(s) of relapse (p=0.1, p=0.3), respectively. There was a significant trend in OS (p=0.001), DFS (p=0.001, and EFS (p=0.001) with higher first remission rates. A total of 16 children who achieved first remission had relapse later in our study. Mean time to relapse was 15.38 months (range:1 month to 29 months). Bone marrow relapse occurred in 15 relapse cases and only there was 1 affected child with a CNS relapse in this study.

Multivariate analysis of prognostic features (age, initial WBC counts, FAB subtype, response to the first course of chemotherapy, CNS involvement, relapse risk, death risk during induction, and DFS) indicated that poor survival was related to age older than 2 years, initial hyperleukocytosis, FAB subtypes other than M3, and more than 15% blasts in bone marrow following the induction chemotherapy. Overall survival was 53% in children with new AML who were on intensive chemotherapy according to BFM-87 protocol with a median follow-up time of 5 years in our study. Relapse risk after the first remission for the children who were on intensive chemotherapy alone was 34% in our study.

Discussion

Although major collaborative groups have demonstrated an improved prognosis for AML[22,23,24,25,16], few publications have concentrated on the specific features of the disease at different ages during childhood [23,26,27,28]. Two studies presented data for children aged under 2 years compared with older children and reported a similar pattern of AML between the first and the second year of life with distinctive features when compared to older children [28,29]. These very young children had high initial WBC counts and an increased incidence of monocytic disease [28,29]. There is a study suggesting that FAB types vary with age with a high incidence of AML M5 and M7 in very young children, whereas the incidence of M0, M1, M2, and M3 increases with age [25]. There has been disagreement regarding the effect of age in childhood on prognosis with both similar [25,32] and poorer outcomes reported compared to older children[26,29,30]. In the series of Vormoor et

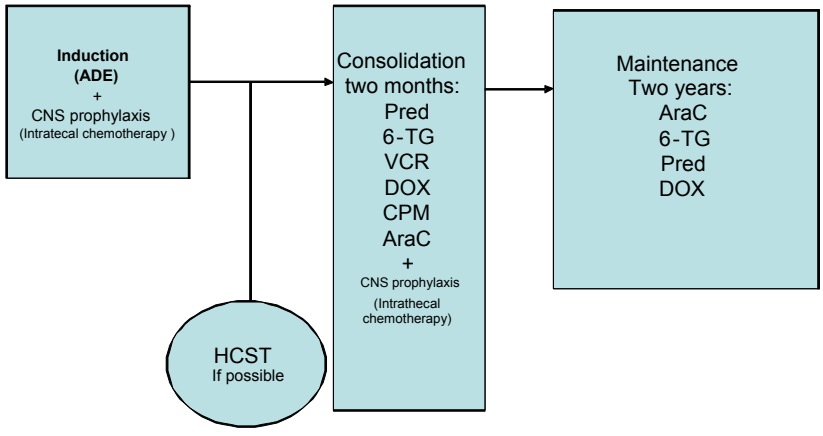

Figure1: *Chemotherapy schedule based on BFM-87 protocol in summary.*

Table 1: *Clinical Features and results*

Parameter	No: (patient) n=47	Age(year) ≤ 2 years n=5	Age(year) > 2 years n=42
Gender:			
male	25	2	23
female	22	3	19
Clinical features:			
fever	44	4	40
hepatosplenomegaly	34	4	30
bone pain	28	2	26
bleeding	25	1	24
Initial WBCs:			
< 50	30	4	26
50-99	9	0	9
100 or above	8	1	7
FAB subtypes:			
M1 (n=2)		0	2
M2 (n=15)		2	13
M3 (n=8)		1	7
M4 (n=14)		2	12
M5 (n=4)		0	4
M6 (n=3)		0	3
M7 (n=1)		0	1
Primary CNS involvement	**3**	0	3
First remission:			
CR (n=42)		5	37
No remission (n=5)		0	5
Deaths	**22**		
Induction deaths (n=13)		0	13
After relapse (n=9)		0	9
Relapse	**16**	0	16
Prognostic Groups:			
Good (n=22)		3	19
Standard (n=10)		1	9
Poor (n=15)		1	14

Table 2. *Outcomes*	**< 2 years**	**> 2 years**
Overall survival (n=25)	5	20
Event-free survival (n=34)	1	33
Disease-free survival (n=18)	4	13

al.,[29] survival was worse in children younger than 2 years due to a resistant disease and relapse, but this was ascribed to the pattern of FAB subtypes because the younger children with FAB subtypes M5 and M7 were identified as carrying poor risk when treated according to Berlin-Frankfurt-Munster (BFM) group protocols[22]. However, in AML 10 and AML 12, FAB type is not included in risk group assignment[32]. An analysis of factors affecting response in AML 10 showed that poor performance status was a risk factor for induction death[32]. Adverse cytogenetics, non-M3 FAB type, and high initial WBC counts were risk factors for a resistant disease, but the effects of FAB subtypes and WBC counts were relatively weak compared to cytogenetics[32]. In our study, there was no difference in remission rates but the resistant disease was less common in younger patients partly counterbalanced by an increase in induction deaths which can be compared to AML 10 and 12 trials.

Following successful induction therapy, relapse was also less common in younger children and there were no differences in deaths in remission, resulting in a better disease-free and overall survival in this study. Multivariate analysis of prognostic factors for children confirmed the importance of cytogenetics, response to the first course of chemotherapy, overall

MRC risk group (a combination of cytogenetics and response to the first course of chemotherapy), and the effects of high initial WBC counts, and demonstrated that age within childhood affected survival, relapse rate, and disease-free survival[29,39].

MRC trials suggest that better control of AML is achieved in these children using treatment of intensity described in that study, irrespective of FAB types[32]. The increased incidence of CNS involvement at the time of diagnosis in younger children and the marginal increase in CNS relapse concurs with other reports[28,29]. Our study showed that age $\leq$ 2 years, FAB type M2 and M4, initial WBC less than 100,000x10^9/L, no CNS involvement, and remission after the first induction chemotherapy improved survival rates due to lower relapse risk and induction deaths. There was no significant risk factor for CNS involvement at the time of the diagnosis of AML or CNS relapse in our study. This is clear that the long-term survival for AML relapse cases is poor and considered to be less than 20% in some large studies whereas the rate of relapse death was 41% for the children who were on intensive chemotherapy alone in our study.

Conclusion

The prognosis of children and adolescents with AML has improved significantly over the past decades[47]. Nowadays, up to 50% of pediatric AML patients experience long-term survival[49,48]. This has been achieved not only by the more effective use of anti-leukemic agents, but also by improvements in HSCT and by better risk-group stratification[47,48,49]. Current risk-group classification is mainly based on cytogenetics and early response to treatment[47]. The overall role of aggressive myelosuppressive chemotherapy for children, adolescents, and young adults with AML is now firmly established[24]. Studies have documented improved overall survival using intensified treatment in induction as well as in the post-remission phase [24]. This aggressive approach, however, is associated with increased morbidity and mortality, primarily related to infection and bleeding from prolonged myelosuppression. For post-remission therapy, there have been 2 major controversies:(1) is the morbidity and mortality associated with graft-versus host disease in allogeneic HSCT worth the potential benefits of graft-versus-leukemia compared with myeloablative approaches not requiring engraftment across histocompatibility barriers? and (2) can aggressive chemotherapy not requiring BMT rescue be as effective as a myeloablative approach with autologous rescue?

One major limitation of previous randomized studies has been the use of less aggressive forms of post-remission chemotherapy compared with current standards [40].

Without some type of post-remission therapy, nearly all patients with AML relapse. Essentially, all patients who do not receive post-remission therapy die from leukemia [33,34,35]. Several studies have strongly suggested that increasing the intensity of immediate post-remission therapy, especially with high-dose cytarabine, has resulted in a lower relapse rate or relapses occurring later in comparison with the patients receiving less intensive maintenance therapy[37,39,17]. Although 75% to 85% of the patients with de novo AML initially achieve remission, only about 50% are long-term survivors with intensive chemotherapy alone [33,17]. Most studies have shown an improved relapsed-free survival in patients with AML who undergo allogeneic HSCT using matched sibling donors [42,44,38,39]. However, in several studies, OS was not initially found to be improved with allogeneic HSCT because of increased treatment-related mortality[19,31]. Randomized trials from the United States and France have consistently shown that HSCT from matched related donors improves DFS, EFS, and OS compared to intensive chemotherapy because of improvements in supportive care and GVHD prophylaxis measures [17]. In contrast, the MRC and BFM group trials did not show a statistically significant advantage for allogeneic HSCT in patients in good or standard risk groups. Thus, allogeneic HSCT from HLA-matched related donors is not offered to these groups in their first CR[39,31,19]. Because of potential morbidity and mortality usually related to allogeneic HSCT and also problems due to lack of sufficient HSCT possibility for some patients, several cooperative group trials do not recommended HSCT for good- or standard- risk patients in their first remission[17,45,46]. Nowadays, many cooperative treatment groups use cytogenetic risk factors for describing risk groups.

Based on many studies, good subgroups include those with t(8;21), inv(16), t(15;17), and Down's syndrome associated AML[17]. However, poor-risk patients are those not in remission after induction therapy or those with monosomy of 5 or 7, del (5q), chromosome 3q abnormalities, or complex karyotypes. It is generally agreed that high-risk patients should receive an allogeneic HSCT if possible [19,31,39,45,46].For good-risk patients, chemotherapy and transplantation results become

closer in terms of overall outcome. Results of our study is compatible in terms of overall survival, relapse risk, and induction death risk factors with BFM , AML 10 and AML 12 groups trials [39,19,31].

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